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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, REBECCA L	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 12/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/509,253	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,14-16 and 18-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *10* is/are allowed.

6)☒ Claim(s) *1-9,14-16 and 18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2004* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/04 and 12/15/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10, 14-16 and 18-21 are currently pending in the instant application. Claim 10 appears allowable over the prior art of record. Claims 1-9, 14-16 and 18-21 are rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15 and 16 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition for the treatment of cataracts which is a calpain and for the method of treating cataracts does not reasonably provide enablement for any pharmaceutical composition which is a calpain inhibitor or for the treatment of any disease in which calpain is involved. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,

2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

In the instant case, claim 15 is a pharmaceutical composition with the intended use as a calpain inhibitor. According to applicants' specification, see page 20, calpain inhibitors are useful for the treatment of various diseases, such as Alzheimer's disease and cataracts, however, the instant specification only provides enablement for a calpain inhibitor for the treatment of cataracts. Claim 16 is drawn to a method of treatment of any disease in which calpain is involved, which includes, for example, Alzheimer's disease. Furthermore, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects and preventive affects of the above listed diseases, whether or not the disease is effected by an inhibitor of calpain would make a difference.

Applicants are claiming pharmaceutical compositions and methods of treating with the formula (I). There is no proof that the claimed compositions have ever been administered to a human (or even to an animal model in the case of most of the diseases) and those skilled in the art would not accept allegations in the instant specification to be reliable predictors of success, and those skilled in the art would not be able to use the compositions of the compounds of the formula (I) since there is no description of an actual method wherein any disease or disorder is treated except the treatment of cataracts.

An example of the high unpredictability of the claimed invention can be seen, for example, by Alzheimer's disease. It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of

acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease.

(<URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html>

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by an inhibitor of calpain, one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of an inhibitor of calpain, since it is known that there is no known cure for Alzheimer's disease and treatment protocols for Alzheimer's disease depend on the stage of the disease.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the listing of diseases applicant considers to be involved with calpain on page 20. There are no working examples present for the treatment of any disease or disorder except cataracts. Assay data and rat tests are found on pages 56-60.

Further, there is no disclosure regarding how all types of the diseases having divers mechanisms are treated. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided of is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for the treatment of any disease in which calpain is involved. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is pharmaceutical compositions of the compound of the formula I and methods of treatment of diseases in which calpain is involved, including Alzheimer's disease. Furthermore, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all diseases would be benefited (treated) by the inhibition of calpain and would furthermore then have to determine which of the claimed compounds would provide treatment of which disease, if any.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to

determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad intended use of the compositions of the instant claims for the treatment of any listed disease or disorder associated with calpain, except cataracts. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the instant claims in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compositions encompassed in the instant claims, with no assurance of success.

This rejection can be overcome by deleting claim 15 and amending claim 16 to only the treatment of cataracts.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 14-16 and 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention. Specifically, claims 1-9, 14-16 and 18-21 have the term "having" or "has" which renders the claims indefinite as the term "having" can be considered open-ended language and therefore is including additional subject matter in the compounds of the claims that is not described in the instant specification and is not particularly pointed out or distinctly claimed. A definition of a chemical compound cannot be open-ended, but must be claimed with precision. The inclusion of the term "having" or "has" includes additional atoms and groups which are not pointed out or distinctly claimed and there is not direction as how to determine the identity of the additional atoms or groups. This rejection can be overcome, for example, by deleting the terms "having" and "has" from the claims such that, for example;

"wherein R1 and R2 are each a lower alkyl group optionally having substituents" could be amended to –wherein R1 and R2 are each optionally substituted lower alkyl--.;

"wherein R1 is a lower alkyl group optionally having substituents" could be amended to –wherein R1 is optionally substituted lower alkyl--;

"wherein R2 is a lower alkyl group having 3 to 4 carbon atoms" could be amended to –wherein R2 is lower alkyl consisting of 3 to 4 carbon atoms--;

"wherein R1 is a lower alkyl group having substituents" could be amended to – wherein R1 is substituted lower alkyl—;

"the lower alkyl group has is an aromatic hydrocarbon group optionally having substituents" could be amended to – wherein the lower alkyl is substituted with an optionally substituted aromatic hydrocarbon--, etc.

Claims 1-9, 14-16 and 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically these claims are drawn to products formula (I) with substituents that contain "groups". The referral to groups in the definition of formula (I) renders the claims indefinite as the groups need only have, for example, a lower alkoxy, but may additionally contain other atoms in the "groups". These other atoms in the compounds of the claims are not described in the instant specification and is not particularly pointed out or distinctly claimed. A definition of a chemical compound cannot be open-ended, but must be claimed with precision. It is suggested that the term "group" be deleted from the claim, such that, for example,

"wherein R1 and R2 are each a lower alkyl group" could be amended to –wherein R1 and R2 are each lower alkyl—;

"wherein R2 is a lower alkyl group substituted by an aromatic hydrocarbon group" could be amended as –wherein R2 is lower alkyl substituted by an aromatic hydrocarbon—'

"wherein the aromatic hydrocarbon group is an aromatic hydrocarbon group substituted by a group selected from the group consisting of a hydroxyl group, a lower alkoxy group, a cyclohexylmethoxy group, a halogen atom and a phenyl group" could be amended as—wherein the optionally substituted aromatic hydrocarbon is substituted with a substituent selected from the group consisting of hydroxyl, lower alkoxy, cyclohexylmethoxy, halogen and phenyl--, etc.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

November 22, 2006

Rebecca Anderson
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